cor et vasa 55 (2013) e212–e216

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Original Research Article

Could severity of mitral annular calcification predict other left sided structural or functional abnormalities?

Ahmed M. Abdel-Salam, Mohamed abdel-Zaher Abdallah*

Cardiology Department, Ain Shams University Hospitals, Ain Shams university Medical School, Cairo, Egypt

ARTICLE INFO

Article history:
Received 20 October 2012
Received in revised form
21 March 2013
Accepted 21 March 2013
Available online 2 April 2013

Keywords:
Mitral annular calcification
Valvular abnormalities
LA systolic function
LA diastolic function
Echocardiography

ABSTRACT

Objective: The prognostic value of MAC severity is important not only because it shares a common risk factors with vascular atherosclerotic changes but also through increasing the cardiovascular morbidity and mortality. This study was conducted in order to evaluate association between severity of MAC and left sided echocardiographic abnormalities mainly left sided valvular abnormalities as well as left atrial systolic and diastolic functional abnormalities.

Methods: We prospectively obtained 12-leads electrocardiograms and transthoracic echocardiograms (TTE) on patients scheduled for non-emergent echocardiographic assessment at tertiary care hospital. MAC was graded as mild, moderate and severe. LA linear dimensions, LA filling and emptying volumes and left atrium ejection fraction were done specifically in addition to commonly measured TTE parameters.

Results: From the 80 patients considered for the study, 47 patients had mild MAC, 29 patients had moderate MAC and 4 patients had severe MAC. Valvular affection through echo-doppler assessment that included mainly mitral stenosis, mitral incompetence, aortic sclerosis as well as aortic incompetence showed a highly significant statistical difference (p-values 0.00, 0.00, 0.00 and 0.00 respectively). There was a highly significant statistical difference between patients with different degrees of MAC and LA linear dimension (p-value 0.00), all LA filling and emptying volumes as well as LA ejection fractions with the exception of LA passive emptying volume and LA passive ejection fraction was insignificant.

Conclusions: There is a direct proportionate relationship between severity of MAC and associated left sided valvular affection, increase LA linear dimension as well as lower overall LA function.

1. Introduction

Mitral annular calcification (MAC) is a well-recognized pathologic entity with unclear etiology in most cases. It represents a chronic, degenerative, non-inflammatory condition in the fibrous base of the mitral valve apparatus [1]. It begins as one or more small hard nodules at the base of the posterior mitral leaflet, commonly the middle of the leaflet. As it increases in

*Correspondance to: Sally Mall, 2nd building, 8th floor, 2 Abdel-Hamyed lofty Street, end of Makram Ebid Street, 8th district, Nasr city, Cairo, Egypt. Tel.: +20 1223247223, +20 226710157; fax: +20 24148622.
E-mail address: ahmedsalam272@gmail.com (A.M. Abdel-Salam).

0010-8650/$ - see front matter © 2013 The Czech Society of Cardiology. Published by Elsevier Urban & Partner Sp.z.o.o. All rights reserved.
http://dx.doi.org/10.1016/j.crvasa.2013.03.013

size, the small calcific nodules coalesce to form a continuous bar or ridge projecting in to the angle between the posterior mitral leaflet and the posterior wall. The calcification occurs in the annulus region and basal part of the leaflets sparing the free edges of the leaflets [2].

Although the development of degenerative calcification of the mitral annulus is functionally of little consequence in most hearts, it shares common risk factors with atherosclerosis; including systemic hypertension, hypercholesterolemia, and diabetes [3]. therefore it is important to risk-stratify patients with MAC because of its association with other important disorders such as coronary and carotid atherosclerosis and increased risk for cardiovascular morbidity and mortality [3,4].

2. Subjects and methods

2.1. Subjects

This was a prospective study conducted on 80 patients with MAC attending for non-emergent echocardiographic assessment at a tertiary care teaching hospital (Ain Shams University Hospitals, Cairo, Egypt). The study protocol was approved by the local ethical committee of Ain Shams University.

Exclusion criteria included age less than 50 years, any metabolic diseases, any significant rheumatic valvular affection as well as patients with atrial fibrillation.

2.2. Methods

Electrocardiogram (ECG) guided trans-thoracic echocardiography (TTE) was performed for determination of the different cardiac cycle phases. The onset of the P wave had been defined as the junction between the isoelectric T-P baseline and the beginning of the P deflection, while the terminal point as the junction between the end of P deflection and the PR segment [5].

Maximal LA linear dimension on TTE had been assessed in the parasternal long axis view from the leading edge of the aortic wall to the leading edge of the posterior LA wall during end systole [6,7]. LA volumes were estimated by applying the method of discs (modified Simpson's rule) to two dimensional apical four and two chamber TTE images [8]. Measurements were obtained during end-systole, end-diastole according to described equations in Table 1 [9,10].

MAC was defined as a dense highly reflective area at the base of the posterior mitral leaflet in the parasternal short axis view [6,7,10]. MAC was graded as none, mild moderate and severe. Mild MAC was cited when one third or less of the mitral annulus was affected, moderate MAC was cited when between one-third and two-thirds of the mitral annulus was

Table 1 – Definitions and formulas for LA volumes[a] and function quantification.

LA vol_{max}	*LA volume in ventricular systole just before mitral valve opening*
LA vol_p	*LA volume before active atrial contraction monitored by P wave onset on ECG*
LA vol_{min}	*minimal LA volume after mitral valve closure*
LA passive emptying volume (*LAPEV*)	$Vol_{max} - Vol_p$
LA active emptying volume (*LAAEV*)	$Vol_p - Vol_{min}$
LA total emptying volume (*LATEV*)	$vol_{max} - vol_{min}$
LA active EF (*LAAEF*)	$LAAEV/vol_p \times 100$
LA total EF (*LATEF*)	$LATEV/vol_{max} \times 100$
LA passive EF (*LAPEF*)	$LAPEV/vol_p \times 100$

[a] LA volume assessed in the apical four- and two-chamber views by applying the methods of discs (modified Simpson's rule).

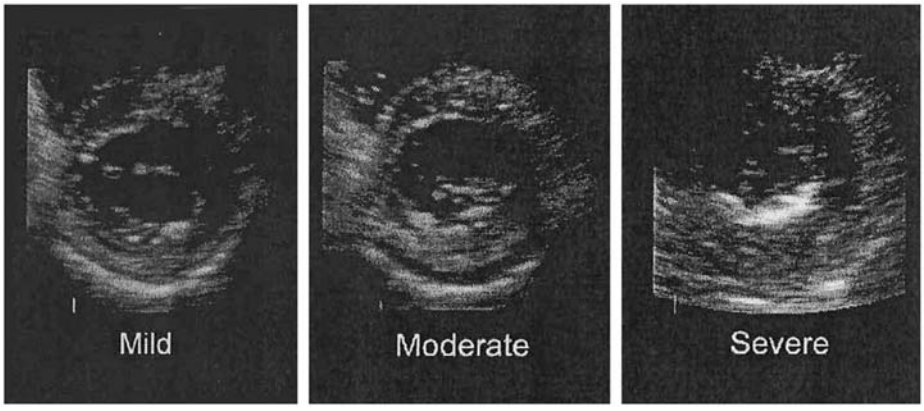

Fig. 1 – Degree of MAC in parasternal short axis view.

affected and severe MAC was cited when involvement exceeded two-thirds of the mitral annulus (Fig. 1) [11].

2.3. Definition of covariates

Baseline evaluation was performed at enrollment. Hypertension status was defined as systolic blood pressure recorded ≥140 mm Hg or a diastolic blood pressure recorded ≥90 mm Hg based on the mean of 2 measurements, a patient's self-reported history of hypertension, or antihypertensive treatment. Diabetes mellitus was defined by a patient's self-reported, insulin use, oral hypoglycemic use, or a fasting glucose ≥126 mg/dl. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Smoking was defined as current cigarette smoking. Echocardiographic parameters and measurements were performed and taken according to the recommendation of the American Society of Echocardiography [11].

2.4. Statistical analysis

The data were coded, entered and processed on computer using Statistical package for Social Science program (SPSS) (version 15) software package under Windows Vista operating system. Student's *t*-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. ANOVA (Analysis of variance) was used to test the difference about mean values of some parameters among multiple groups. Pearson's and Spearman's correlation analysis: assessing the strength of association between two quantitative variables. Chi-square test χ^2 and Fisher's exact test were used to test the categorical variables. The level $p<0.05$ was considered the cut-off value for significance.

Table 2 – Comparison between different degrees of MAC in LA liner dimension.

	LA liner dimension		*ANOVA*	
	Range	*Mean±SD*	*f*	*p-value*
Mild	42–45	43±1.6	**8.633**	**0.00**
Moderate	46–51	49±2.1		
Severe	52–58	54±1.4		
Tukey's test				
Mild and Moderate		*Mild and Severe*	*Moderate and Severe*	
0.03		**0.01**	**0.01**	

3. Results

The three groups were remarkably similar in observed demographic characteristics that include sex, age, weight, height and BMI (*p*-value 0.40, 0.09, 0.25, 0.32 and 0.15 respectively). Also, hypertension and smoking did not show any significant statistical difference (*p*-value 0.06 and 0.58 respectively), diabetes as well as the past history of IHD showed statistical significance when comparing patients with different degree of MAC (*p*-value 0.02 and 0.01 respectively).

The regression analysis of risk factors summation and its correlation to MAC severity showed high statistical significance with *p*-value 0.00 which means that the more the number of risk factors which the patient had, the more will be the expected degree of MAC severity. This reflected from the observation that 50% of severe MAC patients had 3 risk factors and the other 50% had 4 risk factors. On the contrary 95.75% patients with mild MAC had 1 or 2 risk factors while 4.25% had 3 risk factors and none had 4 risk factors.

Valvular affection through echo-doppler assessment that included mainly mitral stenosis, mitral incompetence, aortic sclerosis as well as aortic incompetence showed a highly significant statistical difference (*p*-values 0.00, 0.00, 0.00 and 0.00 respectively). In mild MAC group no one had MS while in moderate MAC group there were 27/29 patients had mild MS and in severe MAC group 50% of patients had mild MS. As regards MR, in mild MAC group there were 10/47 patients who had mild MR, in moderate MAC all patients had mild MR. Among patients with severe MAC, one patient had mild MR and the other 3 patients had moderate MR. The number of patients who had aortic sclerosis were 9/47 patients in mild MAC group, 28/29 in moderate group while all patients in severe MAC group had aortic sclerosis. As regards AR, in mild MAC group there were 6/47 patients who had trivial AR and 3/47 had mild AR. In moderate MAC group there were 6/29 patients who had trivial AR, 19/29 had mild AR and one patient had moderate AR. All patients in severe MAC group had AR, 2 patients with mild AR, and the remaining had moderate AR.

Table 3 – Comparison between different degrees of MAC in LA emptying & filling volumes.

	Mild		Moderate		severe		f-test	*p*-value
	Range	*Mean±SD*	Range	*Mean±SD*	Range	*Mean±SD*		
LA emptying volumes								
LAPEV	11–12	10±0.9	13–14	13.± 0.7	15–16	15±0.3	3.325	**0.05**
LAAEV	12–14	13±1	9–11	10±0.8	6–8	7±0.6	3.325	**0.01**
LA stroke volume	12–14	13±0.5	9–11	10±0.1	6–8	7±0.6	5.325	**0.02**
LATEV	23–25	23±1.1	27–30	28±1.5	31–35	32±1.6	5.325	**0.03**
LA filling volumes								
LA Vol_{max}	49–62	60±1.1	63–73	69±2.1	74–80	77±2.5	6.325	**0.014**
LA Vol_{p}	38–47	42±3.1	48–57	52±3.6	59–70	64.±4.1	15.32	**0.001**
LA Vol_{mini}	24–35	31±2.6	37–49	42±4.7	50–57	53±2.1	9.325	**0.006**
LA volume Index+BMI	32.6–69.4	60±6.6	56.2–103.3	67±10.1	66.6–75.6	70.±3.2	6.253	**0.012**

Table 4 – Comparison between different degrees of MAC in LA ejection fractions.

	Mild		Moderate		Severe		f. test	p-value
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD		
LAPEF	26–30	27±1.5	21–25	22±0.01	17–20	17±1.5	2.214	0.33
LAAEF	25–30	27±1.4	19–24	21±1.7	11–18	15±1.5	4.325	0.01
LATEF	41–46	43±1.7	32–39	35±2.1	24–30	26±2.1	4.265	0.04

Highly significant statistical differences were found between patients with different degrees of MAC and LA linear dimension evaluated by M-mode (*p*-value 0.00) (Table 2). Also, all LA filling and emptying volumes showed a highly significant statistical difference between different groups but LAPEV was insignificant (Table 3). Finally, LA ejection fraction calculated as (LAAEF and LATEF) showed a highly significant statistical difference between different groups. However, LAPEF was insignificant (Table 4).

4. Discussion

MAC was first described when it was noted in association with complete heart block in 1908 [12]. It is a common degenerative process involving the fibrous annulus of the mitral valve, mitral valve leaflets but chordate tendineae are generally not involved [13].

Our study was conducted in order to evaluate association between severity of MAC and left sided echocardiographic abnormalities mainly left sided valvular abnormalities as well as left atrial systolic and diastolic functional abnormalities. We demonstrated that MAC was significantly associated with valvular regurgitation (MR and AR) as well as MS and aortic sclerosis. It is suggested that when mitral valve annulus become thick, rigid and calcified, it may interfere with valve opening and closing, causing valvular stenosis or regurgitation.

When focusing on valvular abnormalities, we discovered a significant association between MAC and presences of MR which increased with severity of MAC. We noticed that moderate MR present only in severe MAC patients while mild MR was noticed both in mild and moderate MAC patients. This goes with a large echocardiographic database of over 24,000 patients conducted in 2007 and evaluated associations between MAC and valvular abnormalities including MR and suggested that MAC became an important cause of mitral regurgitation at severe calcifications [14]. Also, Bozbas et al. stated that MAC occasionally associated with significant mitral regurgitation [15].

As regards mitral stenosis, it was noted to be rare and present in 2.5% of patients. However, we found a strong association between severe degree of MAC and MS (50% of patients). This correlates with Bozbas et al. who reported that MAC can rarely cause symptomatic mitral stenosis that usually present at severe calcification [15] as well as the work done by Salman and colleagues in 2007 at which MS reported to be quite rare [16]. Salman concluded that MAC had reduced mitral valve area compared with normal subjects, and nearly all patients with a significant MV gradient had severe MAC. Also, Korn et al. in 1962 described 14 cases of massive calcification of the mitral annulus of which 9 had significant stenosis [17].

The strong association between MAC and aortic valve calcification in our study suggests that MAC may play a direct role in the pathogenesis of aortic sclerosis or that patients with MAC may represent a group of individuals with increased susceptibility to generalized calcium deposition in the cardiac and extra cardiac tissues. This correlates with Boon et al. who found association between both mitral annular calcification and aortic valve calcification [2].This finding also went with Benjamin et al. who found that patients with mitral annular calcification had a significantly higher prevalence of aortic atheroma [18].

A direct proportional relationship between severity of MAC and LA enlargement was demonstrated. It is suggested that this enlargement may be as a cumulative effect of associated risk factors, presence of valvular abnormalities as well as the strong correlations between MAC and IHD. All these factors can either directly or indirectly enhance stress on the LA resulting in its enlargement. Ariyarajah et al. on the other hand, reported the same association between MAC and increase in LA linear dimension [19].

LA systolic volume, which in essence, represents the volume emptied from the LA following active atrial contraction, was lower as we expand from mild to severe MAC. There was a trend toward lower (LASV), LAAEF as well as LATEF with increasing severity of MAC. This results in a poorer LA active emptying fraction and serves as a good indicator of a poor overall LA function. Lower LA stroke volumes and emptying fractions may not be as much of a factor in those with preserved left ventricular function or those without severe left ventricular diastolic impairment [20]. However, in vulnerable patients who are dependent on intact atrial function, such as those with severely depressed left ventricular systolic or diastolic function they may add to a greater compromise in already depressed cardiac output [20,21].

We could not find any paper that demonstrates severe MAC as a separate entity and compares it with mild and moderate degree which may be due to rarity of this finding. In our study we found 4 patients (5%) with severe MAC and concluded that the more the severity of MAC, the more the increase in LA dimension, the more the decrease in LA ejection fractions as well as the higher the incidence of valvular affection especially MR and aortic sclerosis.

REFERENCES

[1] Y. Adler, N. Fink, D. Spector, et al., Mitral annulus calcification – a window to diffuse atherosclerosis and cardiovascular risk factors, Atherosclerosis 155 (2001) 1–8.

[2] A. Boon, E. Cheriex, J. Lodder, F. Kessels, Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve, Heart 78 (1997) 472–474.
[3] C.S. Fox, R.S. Vasan, H. Parise, et al., Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study, Circulation 107 (11) (2003) 1492–1496.
[4] D.S. Jeon, S. Atar, A.V. Brasch, et al., Association of mitral annular calcification, aortic valve sclerosis and aortic root calcification with abnormal myocardial perfusion single photon emission tomography in subject age < or = 65 years old, Journal of the American College of Cardiology 38 (7) (2001) 1988–1993.
[5] A. Bayes de Luna, Electrocardiographic alterations due to atrial pathology, in: A. Bayes de Luna (Ed.), Clinical Electrocardiography: A Textbook, Futura Company Inc., New York, 1998, pp. 169–171.
[6] J.K. Oh, J.B. Seward, A.J. Tajok (Eds.), The Echo Manual, 2nd Ed, Lippincott-Williams and Wilkins, Philadelphia, 1999.
[7] M.D. Cheitlin, W.F. Armstrong, G.P. Aurigemma, et al., ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography), Journal of the American Society of Echocardiography 16 (2003) 1091–1110.
[8] S.B. Goyal, D.H. Spodick, Electromechanical dysfunction of the left atrium associated with interatrial block, American Heart Journal 142 (2001) 823–827.
[9] H.T. Dodge, H. Sandler, D.W. Ballew, J.D. Lord, The use of biplane angiocardiography for the measurement of left ventricular volume in man, American Heart Journal 60 (1960) 762–776.
[10] M. Wong, C. Tei, P.M. Shah, Sensitivity and specificity of two dimensional echocardiography in the detection of valvular calcification, Chest 84 (1983) 423–427.
[11] R.M. Lang, M. Bierig, R.B. Devereux, et al., Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee, and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology, Journal of the American Society of Echocardiography 18 (2005) 1440–1463.
[12] M. Bonninger, (a) Bluttransfusion bei pernizioser anamie: (b) Zwei Falle von Herzblock, Deutsche Medizinische Wochenschrift 34 (1908) 2292.
[13] D. Harpaz, I. Auerbach, Z. Vered, et al., Caseous calcification of the mitral annulus: a neglected, unrecognized diagnosis, Journal of the American Society of Echocardiography 14 (2001) 825–831.
[14] M. Movahed, Y. Siato, M. Ahmadi-Kashani, R. Ebrahimi, Mitral annulus calcification is associated with valvular and cardiac structural abnormalities, Cardiovascular Ultrasound 5 (2007) 14.
[15] H. Bozbas, B. Pirat, A. Yildirir, et al., Mitral annular calcification associated with impaired coronary microvascular function, Atherosclerosis 198 (2008) 115–121.
[16] S.M. Muddassir, S. Gregg, Mitral annular calcification as a cause of mitral valve gradients, International Journal of Cardiology 123 (2007) 58–62.
[17] D. Korn, R.W. DeSanctis, S. Sell, Massive calcification of the mitral annulus. A clinicopathologic study of fourteen cases, The New England Journal of Medicine 267 (1962) 900–909.
[18] E.J. Benjamin, J.F. Plehn, R.B. D'Agostino, et al., Mitral annular calcification and the risk of stroke in an elderly cohort, The New England Journal of Medicine 327 (1992) 374–379.
[19] V. Ariyarajah, S. Apiyasawat, I. Barac, D.H. Spodick, Is the presence of mitral annular calcification associated with poor left atrial function, Echocardiography 26 (8) (2009) 877–884.
[20] Y. Adler, U. Levinger, A. Koren, et al., Association between mitral annulus calcification and peripheral arterial atherosclerotic disease, Angiology 51 (2005) 639–646.
[21] H.J. Willens, J.A. Chirinos, A. Schob, et al., The relation between mitral annular calcification and mortality in patients undergoing diagnostic coronary angiography, Echocardiography 23 (2006) 717–722.